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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/680,576	10/06/2003	Steven F. Dowdy	47275-C (71742)	5251

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EXAMINER	
GARVEY, TARA L	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 11/30/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	**Application No.** 10/680,576	**Applicant(s)** DOWDY ET AL.	
	Examiner Tara L. Garvey	**Art Unit** 1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 September 2005*.
2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.
3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *36-51* is/are pending in the application.
  4a) Of the above claim(s) *38, 41 and 44* is/are withdrawn from consideration.
5)☐ Claim(s) _____ is/are allowed.
6)☒ Claim(s) *36, 37, 39, 40, 42, 43 and 45-51* is/are rejected.
7)☐ Claim(s) _____ is/are objected to.
8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.
10)☒ The drawing(s) filed on *06 October 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.
  Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
  Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
  a)☐ All b)☐ Some * c)☐ None of:
    1.☐ Certified copies of the priority documents have been received.
    2.☐ Certified copies of the priority documents have been received in Application No. _____.
    3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
  * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)	4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)	5) ☐ Notice of Informal Patent Application (PTO-152)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/2/04*.	6) ☒ Other: *Notice to comply*.

DETAILED ACTION

Receipt is acknowledged of a preliminary amendment filed on December 1, 2003 in which claims 1-35 were canceled and new claims 36-51 were added. Claims 36-51 are pending.

Election/Restrictions

Claims 38 and 39-51 only as they depend to claim 38 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on September 6, 2005.

Applicant's election with traverse of Group I (claims 36-37 and 39-51 as they depend form 36-37) in the reply filed on September 6, 2005 is acknowledged. The traversal is on the ground(s) that an undue search burden does not exist because the searches of the two groups would overlap significantly. This is not found persuasive because the inventions are distinct and a search burden exists. While searches may partially overlap, they also extend beyond one another. In the case of the two methods, a reference may exist that teaches the method of Group I and not the method of Group II since the steps of each method differ.

The requirement is still deemed proper and is therefore made FINAL.

Sequence Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth below.

In the Drawings, Figures 1 and 2 contain sequences, but do not have any sequence identifiers either in the figure or in the Brief Description of the Drawings.

In response to this office action, Applicant must comply with the sequence rules, 37 CFR 1.821 - 1.825. Please amend the Brief Description of the Drawings to recite the corresponding SEQ ID NOs. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR 1.821(g). The nature of the non-compliance did not preclude an examination of the elected invention on the merits, the results of which are presented below.

Specification

Please update the specification to recite that "This application is a continuation of application 09/134,793 filed on August 14, 1998, now abandoned."

The disclosure is objected to because of the following informalities: The disclosure appears to be missing the last page of the specification since the last sentence on page 19 does not end with a punctuation mark and because the specification in the application 09/134,793 to which the instant application claims priority has an additional page.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 37, 39, 40, 42, 43 and 45-51 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.**

Claims 36, 37, 39, 40, 42, 43 and 45-51 are drawn to a method of screening the effect of a compound of interest on cell comprising contacting a first cell that comprises a DNA encoding the compound or interest operably linked to a regulatory sequence with a fusion protein that comprises a protein transduction domain from TAT and a transcriptional activator region that binds to the regulatory sequence to induce DNA expression. As controls, contacting a second cell with no protein or a protein that lacks a protein transduction domain, a transcription activator region or both or contacting a second which does not comprise the DNA encoding the compound or interest operably linked to a regulatory sequence or an RNA polymerase required for expression of said DNA, or both with a fusion protein. The phenotypes of the two cells are compared and the difference in the phenotypes is the effect of the compound on the cell.

The specification describes a method to screen the effect of a compound that comprises contacting a first cell that comprises a DNA encoding a compound of interest operably linked to a regulatory sequence with a fusion protein. The fusion protein comprises a protein transduction domain from TAT and a transcriptional activator region that binds to the regulatory sequence to induce DNA expression.

The specification does not describe all the all the limitations of the second cell which serves as the control cell in the method of screening compounds. The specification does not describe introducing into a second cell a protein that does not comprise a transduction domain as a species of the type of control proteins that can be added to the second cell in claim 36 and therefore constitutes new matter. The specification does not describe a method in which a second cell which does not comprise the DNA encoding the compound of interest operably linked to a regulatory sequence or an RNA polymerase required for expression of said DNA, or both is contacted with the fusion protein and therefore constitutes new matter. Thus, the new limitations present in claims 36 and 37 constitute new matter.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 36, 42, 43, 45-48, 50, 51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bujard et al (US 5,589,362 as cited in the IDS submitted on November 2, 2004) in view of Frankel et al (US 5,652,122 as cited in the IDS submitted on November 2, 2004) and Basset et al (US 6,184,256).

Bujard et al teach expression systems comprising transfecting into a cell an expression system comprising a vector that expresses a transactivator fusion protein comprising a transcriptional activation domain such amino acids 753-881 of Gal4, a DNA binding domain such as Gal4 binding domain, and a polypeptide which promotes transport of the fusion protein to the nucleus, and a vector comprising a heterologous gene operatively linked to a regulatory sequence to which the fusion protein binds (column 4, lines 58-67, columns 5-8, column 9, lines 62-67 bridging column 10, lines 1-7, column 10, lines 60-67 bridging column 11, column 16, lines 45-48). The fusion protein can comprise a putative transcriptional activation domain and the Gal4 DNA binding domain, which reads on a fusion protein in which the DNA binding domain and the transactivation domain are from different proteins (column 10, lines 25-31). Brujard et al also teach that eukaryotic or mammalian cell lines in the method (columns 13-14). This reference also teaches that the expression system is widely applicable to a variety of situations where it is desirable to be able to turn on gene expression on and off, or regulate the level of gene expression, such as study of cellular development ad differentiation in cells, for example, regulating in a controlled manner expression of oncogenes to study their function (column 35, lines 52-61).

Bujard et al do not specifically teach contacting a cell with a fusion protein comprising a protein transduction domain or comparing the first cell to a second control cell that has not been contacted with a functional protein or does not express the compound of interest

Frankel et al teach a way of introducing proteins into a cell that is an alternative to the normal means for delivering macromolecules into cells, such as delivering nucleic acids by transfection and transformation into a cell, followed by their expression (abstract, columns 1-4). The method taught by Frankel et al is the linkage of a protein transduction domain taught by the reference such as the tat-derived sequence with or without additional amino acid changes to the protein desired to be in the cell, followed by contacting the cell with the fusion protein (columns 1-6, column 7, lines 1-62, column 9, lines 9-46, column 12, lines 12-67, columns 13-14). This reference specifically teaches that the method is useful as a means of delivering into the nucleus substances whose effect on cell function is to be assessed, such as a regulatory factor like a transcription factor (columns 12 and 14). Frankel et al teach that this method more efficiently delivers biologically active proteins into cells than the previous methods used in the art (columns 1-2).

Basset et al teaches a method of screening for the effect of a composition on the expression of a gene in a cell in which the first cell is contacted with the composition, but the second cell is not and then the levels of gene expression are compared between the first and second cell to determine the effect of the composition on gene expression (column 10, lines 19-41 and column 11, lines 27-67 bridging column 12).

It would have been obvious to one of ordinary skill in the art at the time of the invention was made to use the protein transduction domain taught by Frankel et al in the fusion protein taught by Bujard et al in the method of screening compounds where the phenotypes of a cell with the fusion protein and a cell without the fusion protein is compared to determine the effect of the compound on a cell because Frankel et al teach that it is within the ordinary skill in the art to do so for regulatory proteins that are desired to be delivered to the nucleus as an alternative to prior art nucleic acid delivery methods used to delver nucleic acids that express the protein. It would have been further obvious to use the resulting expression system of a DNA encoding a compound of interest in a cell and determining the effects of the expression because Bujard et al teach that the expression system is widely applicable to a variety of situations where it is desirable to be able to turn gene expression on and off, or regulate the level of gene expression, such as the study of cellular development and differentiation of cells, for example, regulating in a controlled manner expression of oncogenes to study their function, Frankel et al teach that the (protein transduction) method is useful as a means of delivering into the nucleus substances whose effect on cell function is to be assessed, such as a regulatory factor and Basset et al teach that a "control" treated cell is needed to determine the effect of the compound on a cell in a method of screening compounds. One would have been motivated to do so for the expected benefit of more efficiently delivering biologically active proteins into cells for use in the assay, as taught by Frankel et al and being able to determine the effect of the delivery of the compound by comparing the result in a control cell. From the teachings of the cited references showing successful applications of their respective methods and absent of evidence to the contrary, there would have been a reasonable expectation of success that the resulting assay method would have been functional.

Claim 36, 42, 43, 45-51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bujard et al, Frankel et al and Basset et al (US 6,184,256) as applied to claims 36, 42, 43, 45-48, 50, 51 above, and further in view of Bonifaci et al (AIDS (1995) volume 9, page 995-1000 as cited on the IDS submitted November 2, 2004).

Bujard et al, Frankel et al and Basset et al are all taught above.

Bujard et al and Frankel et al do not specifically teach partially denaturing the fusion protein when it is introduced into the cell.

Bonafaci et al teach that exogenous internalization by Tat requires unfolding (which naturally occurs as it goes into the cell) (page 999).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to partially denature the fusion protein in the expression system made from the combined teachings of Bujard et al and Frankel et al because Bonifaci et al teach that exogenous internalization requires unfolding and it is within the ordinary skill in the art to partially denature proteins in order to unfold them. Alternatively, it would have been obvious to allow the fusion protein to naturally denature as a part of its normal unfolding process as it introduced into the cell, using the inherent process as taught by Bonifaci et al. One would have been motivated to do so either way for the expected benefit of aiding or allowing natural exogenous internalization of the fusion protein as taught by Bonifaci et al. From the teachings of the cited references and absent evidence to the contrary, there would have been a reasonable expectation of success that partially denaturing the fusion protein or allowing the natural process to occur would be successful in exogenous internalization as taught by Bonifaci et al.

Claim 36, 39, 40, 42, 43, 45-51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bujard et al, Frankel et al and Basset et al (US 6,184,256) as applied to claims 36, 42, 43, 45-48, 50, 51 above, and further in view of Cheng et al (US 5,674, 898).

Bujard et al, Frankel et al and Basset et al are all taught above.

Bujard et al and Frankel et al do not specifically teach using the T7 RNA polymerase promoter as the regulatory sequence that is linked to the DNA encoding the heterologous gene.

Cheng et al teach that the T7 RNA polymerase promoter can be used in an inducible expression system to induce the transcription of a gene (column 16, lines 52-66).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the T7 RNA polymerase promoter as the regulatory sequence in the expression system made from the combined teachings of Bujard et al and Frankel et al because Cheng et al teach that the T7 RNA polymerase is a suitable promoter to use for induce transcription in an inducible expression system. One would have been motivated to do so either way for the expected benefit of obtaining expression of the heterologous gene at a desired time from a reliable promoter. From the teachings of the cited references and absent evidence to the contrary, there would have been a reasonable expectation of success that the T7 RNA polymerase promoter would be successful in driving the expression of the heterologous gene upon induction as taught by Cheng et al.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tara L Garvey whose telephone number is (571) 272-

2917. The examiner can normally be reached on Monday through Friday 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) (http://pair-direct.uspto.gov) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

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Tara L Garvey
Examiner
Art Unit 1636

TLG

DANIEL M. SULLIVAN
PATENT EXAMINER

Notice to Comply	Application No. 10/680,576	Applicant(s) Dowdy et al
	Examiner Tara L. Garvey	Art Unit 1636

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set in the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☒ 7. Other: Sequences in Figures 1 and 2 should be identified by sequence identifiers.

Applicant Must Provide:

☐ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☐ An initial or substitute paper copy of the "Sequence Listing", **as well as an amendment specifically directing its entry into the specification**.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

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